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Subject: articles

Please provide the following articles ASAP. thanks!
Serial No. 09/685,696.

L10 ANSWER 65 OF 70 MEDLINE on STN DUPLICATE 29
AU Maloy K J; Donachie A M; Mowat A M
TI Induction of Th1 and Th2 CD4+ T cell responses by oral or parenteral immunization with ISCOMS.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Oct) 25 (10) 2835-41.

L10 ANSWER 62 OF 70 MEDLINE on STN DUPLICATE 27
AU Sjolander A; van't Land B; Lovgren Bengtsson K
TI Iscoms containing purified Quillaja saponins upregulate both Th1-like and Th2-like immune responses.
SO CELLULAR IMMUNOLOGY, (1997 Apr 10) 177 (1) 69-76.

L10 ANSWER 58 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU Sjolander A (Reprint); Bengtsson K L; Morein B
TI Kinetics, localization and cytokine profile of T cell responses to immune stimulating complexes (iscoms) containing human influenza virus envelope glycoproteins
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L10 ANSWER 56 OF 70 MEDLINE on STN DUPLICATE 22
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SO JOURNAL OF CONTROLLED RELEASE, (1998 Jun) 54 (1) 49-59.

L10 ANSWER 40 OF 70 MEDLINE on STN DUPLICATE 14
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SO JOURNAL OF IMMUNOLOGY, (1999 Feb 15) 162 (4) 2251-8.

L10 ANSWER 39 OF 70 MEDLINE on STN DUPLICATE 13
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SO VACCINE, (1999 Jun 4) 17 (20-21) 2517-27.

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     (FILE 'HOME' ENTERED AT 19:17:37 ON 12 NOV 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 19:17:53 ON 12 NOV
     2003
L1          6254 S MONOPHOSPHORYL(W)LIPID(W)A OR QS21 OR MONTANIDE(W)ISA(W)720 O
L2            19 S AMINOALKYL(W)GLUCOSAMINIDE(W)4-PHOSPHATE
L3          6263 S L1 OR L2
L4             1 S ADUVANT AND L3
L5          2011 S ADJUVANT AND L3
L6         16142 S TH1(6A)RESPONSE
L7           146 S L5 AND L6
L8           146 S L5(10A)L6
L9           146 S L5(S)L6
L10           70 DUP REM L9 (76 DUPLICATES REMOVED)

=> d au ti so 30-70 l10

L10  ANSWER 30 OF 70     MEDLINE on STN                  DUPLICATE 10
AU   Aebischer T; Wolfram M; Patzer S I; Ilg T; Wiese M; Overath P
TI   Subunit vaccination of mice against new world cutaneous leishmaniasis:
     comparison of three proteins expressed in amastigotes and six
     adjuvants.
SO   INFECTION AND IMMUNITY, (2000 Mar) 68 (3) 1328-36.
     Journal code: 0246127. ISSN: 0019-9567.

L10  ANSWER 31 OF 70     MEDLINE on STN                  DUPLICATE 11
AU   da Fonseca D P; Frerichs J; Singh M; Snippe H; Verheul A F
TI   Induction of antibody and T-cell responses by immunization with
     ISCOMS containing the 38-kilodalton protein of Mycobacterium
     tuberculosis.
SO   VACCINE, (2000 Aug 15) 19 (1) 122-31.
     Journal code: 8406899. ISSN: 0264-410X.

L10  ANSWER 32 OF 70  CAPLUS  COPYRIGHT 2003 ACS on STN
IN   Bruck, Claudine Elvire Marie; Cassart, Jean-Pol; Coche, Thierry;
     Vinals-Bassols, Carlota
TI   Protein and cDNA sequences of human homolog (CASB47) to mouse PAP-1, and
     uses thereof in diagnosis and therapy for tumors and autoimmune diseases
SO   PCT Int. Appl., 56 pp.
     CODEN: PIXXD2

L10  ANSWER 33 OF 70  CAPLUS  COPYRIGHT 2003 ACS on STN
IN   Stephenne, Jean; Wettendorff, Martine Anne Cecile
TI   Combined vaccine compositions
SO   PCT Int. Appl., 39 pp.
     CODEN: PIXXD2

L10  ANSWER 34 OF 70  CAPLUS  COPYRIGHT 2003 ACS on STN
IN   Cabezon, Silva Teresa; Cohen, Joseph; Slaoui, Moncef Mohamed; Vinals
     Bassols, Carlota
TI   Tumor-associated antigen derivatives of MAGE proteins and their use in
     cancer vaccine therapy
SO   PCT Int. Appl., 74 pp.
     CODEN: PIXXD2

L10  ANSWER 35 OF 70  CAPLUS  COPYRIGHT 2003 ACS on STN
IN   Bruck, Claudine; Bollen, Alex; Jacobs, Paul; Massaer, Marc
TI   Recombinant vaccine containing mutant Der P1 allergen with reduced
     enzymatic activity
SO   PCT Int. Appl., 46 pp.
     CODEN: PIXXD2
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L10 ANSWER 36 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
IN Bruck, Claudine; Cabezon Silva, Teres; Delisse, Anne-Marie Eva Fernande; Gerard, Catherine Marie Ghislaine; Lombardo-Bencheikh, Angela
TI Fusion proteins of human papillomavirus E6 and E7 stimulate a type 1 T-cell response
SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2

L10 ANSWER 37 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
IN Walker, Bruce D.
TI Method of eliciting anti-HIV-1 helper T cell responses
SO U.S., 25 pp.
CODEN: USXXAM

L10 ANSWER 38 OF 70 MEDLINE on STN DUPLICATE 12
AU Abuodeh R O; Shubitz L F; Siegel E; Snyder S; Peng T; Orsborn K I; Brummer E; Stevens D A; Galgiani J N
TI Resistance to Coccidioides immitis in mice after immunization with recombinant protein or a DNA vaccine of a proline-rich antigen.
SO INFECTION AND IMMUNITY, (1999 Jun) 67 (6) 2935-40.
Journal code: 0246127. ISSN: 0019-9567.

L10 ANSWER 39 OF 70 MEDLINE on STN DUPLICATE 13
AU Moore A; McCarthy L; Mills K H
TI The **adjuvant** combination **monophosphoryl lipid A** and **QS21** switches T cell responses induced with a soluble recombinant HIV protein from Th2 to Th1.
SO VACCINE, (1999 Jun 4) 17 (20-21) 2517-27.
Journal code: 8406899. ISSN: 0264-410X.

L10 ANSWER 40 OF 70 MEDLINE on STN DUPLICATE 14
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TI TCR vaccines against T cell lymphoma: QS-21 and IL-12 **adjuvants** induce a protective CD8+ T cell response.
SO JOURNAL OF IMMUNOLOGY, (1999 Feb 15) 162 (4) 2251-8.
Journal code: 2985117R. ISSN: 0022-1767.

L10 ANSWER 41 OF 70 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AU Jiang, Baoming [Reprint author]; Estes, Mary K.; Barone, Christopher; Barniak, Vicki; O'Neal, Christine M.; Ottaiano, Adriana; Madore, H. Paul; Conner, Margaret E.
TI Heterotypic protection from rotavirus infection in mice vaccinated with virus-like particles.
SO Vaccine, (Feb., 1999) Vol. 17, No. 7-8, pp. 1005-1013. print.
CODEN: VACCDE. ISSN: 0264-410X.

L10 ANSWER 42 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Heeney, Jonathan; Akerblom, Lennart; Barnett, Susan; Bogers, Willy; Davis, David; Fuller, Deborah; Koopman, Gerrit; Lehner, Thomas; Mooij, Petra; Morein, Bror; de Giuli Morghen, Carlo; Rosenwirth, Brigitte; Verschoor, Ernst; Wagner, Ralf; Wolf, Hans
TI HIV-1 vaccine-induced immune responses which correlate with protection from SHIV infection: compiled preclinical efficacy data from trials with ten different HIV-1 vaccine candidates
SO Immunology Letters (1999), 66(1-3), 189-195
CODEN: IMLED6; ISSN: 0165-2478

L10 ANSWER 43 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 15
AU Haigwood, Nancy L.; Pierce, Christopher C.; Robertson, Michael N.; Watson, Andrew J.; Montefion, David C.; Rabin, Michael; Lynch, John B.; Kuller, LaRene; Thompson, Jannelle; Morton, William R.; Benveniste, Raoul E.; Hu, Shiu-Lok; Greenbag, Philip; Mossman, Sally P.
TI Protection from pathogenic SIV challenge using multigenic DNA vaccines
SO Immunology Letters (1999), 66(1-3), 183-188

CODEN: IMLED6; ISSN: 0165-2478

L10 ANSWER 44 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU Rajananthanan P; Attard G S; Sheikh N A; Morrow W J W (Reprint)
TI Novel aggregate structure **adjuvants** modulate lymphocyte proliferation and Th1 and Th2 cytokine profiles in ovalbumin immunized mice
SO VACCINE, (20 AUG 1999) Vol. 18, No. 1-2, pp. 140-152.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 0264-410X.

L10 ANSWER 45 OF 70 MEDLINE on STN DUPLICATE 16
AU Mowat A M; Smith R E; Donachie A M; Furrie E; Grdic D; Lycke N
TI Oral vaccination with immune stimulating complexes.
SO IMMUNOLOGY LETTERS, (1999 Jan) 65 (1-2) 133-40.
Journal code: 7910006. ISSN: 0165-2478.

L10 ANSWER 46 OF 70 MEDLINE on STN DUPLICATE 17
AU Morein B; Bengtsson K L
TI Immunomodulation by **iscoms**, immune stimulating complexes.
SO METHODS, (1999 Sep) 19 (1) 94-102. Ref: 88
Journal code: 9426302. ISSN: 1046-2023.

L10 ANSWER 47 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Van Pinxteren, Laurens A. H.; Bruce, Maureen G.; Campbell, Iris; Wood, Ann; Clarke, Christopher J.; Bellman, Anna; Morein, Bror; Snodgrass, David R.
TI Effect of oral rotavirus/iscom vaccines on immune responses in gnotobiotic lambs
SO Veterinary Immunology and Immunopathology (1999), 71(1), 53-67
CODEN: VIIMDS; ISSN: 0165-2427

L10 ANSWER 48 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
IN Cohen, Joseph
TI Vaccine composition against malaria
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2

L10 ANSWER 49 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Sasaki, Shin; Sumino, Kaharu; Hamajima, Kenji; Fukushima, Jun; Ishii, Norihisa; Kawamoto, Susumu; Mohri, Hiroshi; Kensil, Charlotte Read; Okuda, Kenji
TI Induction of systemic and mucosal immune responses to human immunodeficiency virus type 1 by a DNA vaccine formulated with QS-21 saponin **adjuvant** via intramuscular and intranasal routes
SO Journal of Virology (1998), 72(6), 4931-4939
CODEN: JOVIAM; ISSN: 0022-538X

L10 ANSWER 50 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Sjolander, Anders; Baldwin, Tracey M.; Curtis, Joan M.; Handman, Emanuela
TI Induction of a **Th1** immune **response** and simultaneous lack of activation of a Th2 response are required for generation of immunity to leishmaniasis
SO Journal of Immunology (1998), 160(8), 3949-3957
CODEN: JOIMA3; ISSN: 0022-1767

L10 ANSWER 51 OF 70 MEDLINE on STN DUPLICATE 18
AU Sjolander A; Baldwin T M; Curtis J M; Bengtsson K L; Handman E
TI Vaccination with recombinant Parasite Surface Antigen 2 from Leishmania major induces a **Th1** type of immune **response** but does not protect against infection.
SO VACCINE, (1998 Dec) 16 (20) 2077-84.
Journal code: 8406899. ISSN: 0264-410X.

L10 ANSWER 52 OF 70 MEDLINE on STN DUPLICATE 19
AU Newman K D; Sosnowski D L; Kwon G S; Samuel J
TI Delivery of MUC1 mucin peptide by Poly(d,l-lactic-co-glycolic acid) microspheres induces type 1 T helper immune responses.
SO JOURNAL OF PHARMACEUTICAL SCIENCES, (1998 Nov) 87 (11) 1421-7.
Journal code: 2985195R. ISSN: 0022-3549.

L10 ANSWER 53 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Papadopoulou, Georgia; Karagouni, Evdokia; Dotsika, Eleni
TI **ISCOMs** vaccine against experimental leishmaniasis
SO Vaccine (1998), 16(9/10), 885-892
CODEN: VACCDE; ISSN: 0264-410X

L10 ANSWER 54 OF 70 MEDLINE on STN DUPLICATE 20
AU Morein F; Bengtsson K L
TI Functional aspects of **iscoms**.
SO IMMUNOLOGY AND CELL BIOLOGY, (1998 Aug) 76 (4) 295-9. Ref: 29
Journal code: 8706300. ISSN: 0818-9641.

L10 ANSWER 55 OF 70 MEDLINE on STN DUPLICATE 21
AU Smith R E; Donachie A M; Mowat A M
TI Immune stimulating complexes as mucosal vaccines.
SO IMMUNOLOGY AND CELL BIOLOGY, (1998 Jun) 76 (3) 263-9. Ref: 63
Journal code: 8706300. ISSN: 0818-9641.

L10 ANSWER 56 OF 70 MEDLINE on STN DUPLICATE 22
AU Newman K D; Samuel J; Kwon G
TI Ovalbumin peptide encapsulated in poly(d,l lactic-co-glycolic acid) microspheres is capable of inducing a T helper type 1 immune response.
SO JOURNAL OF CONTROLLED RELEASE, (1998 Jun) 54 (1) 49-59.
Journal code: 8607908. ISSN: 0168-3659.

L10 ANSWER 57 OF 70 MEDLINE on STN DUPLICATE 23
AU Morein B; Villacres-Eriksson M; Lovgren-Bengtsson K
TI Iscom, a delivery system for parenteral and mucosal vaccination.
SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1998) 92 33-9. Ref: 16
Journal code: 0427140. ISSN: 0301-5149.

L10 ANSWER 58 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU Sjolander A (Reprint); Bengtsson K L; Morein B
TI Kinetics, localization and cytokine profile of T cell responses to immune stimulating complexes (**iscoms**) containing human influenza virus envelope glycoproteins
SO VACCINE, (JUN 1997) Vol. 15, No. 9, pp. 1030-1038.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, OXON, ENGLAND OX5 1GB.
ISSN: 0264-410X.

L10 ANSWER 59 OF 70 MEDLINE on STN DUPLICATE 24
AU Ahluwalia A; Gokulan K; Nath I; Rao D N
TI Modification of delivery system enhances MHC nonrestricted immunogenicity of V3 loop region of HIV-1 gp120.
SO MICROBIOLOGY AND IMMUNOLOGY, (1997) 41 (10) 779-84.
Journal code: 7703966. ISSN: 0385-5600.

L10 ANSWER 60 OF 70 MEDLINE on STN DUPLICATE 25
AU Dotsika E; Karagouni E; Sundquist B; Morein B; Morgan A; Villacres-Eriksson M
TI Influence of Quillaja saponaria triterpenoid content on the immunomodulatory capacity of Epstein-Barr virus **iscoms**.
SO SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1997 Mar) 45 (3) 261-8.
Journal code: 0323767. ISSN: 0300-9475.

L10 ANSWER 61 OF 70 MEDLINE on STN DUPLICATE 26
AU Villacres-Eriksson M; Behboudi S; Morgan A J; Trinchieri G; Morein B
TI Immunomodulation by Quillaja saponaria **adjuvant** formulations: in vivo stimulation of interleukin 12 and its effects on the antibody response.
SO CYTOKINE, (1997 Feb) 9 (2) 73-82.
Journal code: 9005353. ISSN: 1043-4666.

L10 ANSWER 62 OF 70 MEDLINE on STN DUPLICATE 27
AU Sjolander A; van't Land B; Lovgren Bengtsson K
TI **Iscoms** containing purified Quillaja saponins upregulate both **Th1**-like and Th2-like immune **responses**.
SO CELLULAR IMMUNOLOGY, (1997 Apr 10) 177 (1) 69-76.
Journal code: 1246405. ISSN: 0008-8749.

L10 ANSWER 63 OF 70 MEDLINE on STN DUPLICATE 28
AU Noll A; AutenriethIB
TI Immunity against Yersinia enterocolitica by vaccination with Yersinia HSP60 immunostimulating complexes or Yersinia HSP60 plus interleukin-12.
SO INFECTION AND IMMUNITY, (1996 Aug) 64 (8) 2955-61.
Journal code: 0246127. ISSN: 0019-9567.

L10 ANSWER 64 OF 70 MEDLINE on STN
AU Gupta R K; Varanelli C L; Griffin P; Wallach D F; Siber G R
TI **Adjuvant** properties of non-phospholipid liposomes (Novasomes) in experimental animals for human vaccine antigens.
SO VACCINE, (1996 Feb) 14 (3) 219-25.
Journal code: 8406899. ISSN: 0264-410X.

L10 ANSWER 65 OF 70 MEDLINE on STN DUPLICATE 29
AU Maloy K J; Donachie A M; Mowat A M
TI Induction of **Th1** and Th2 CD4+ T cell **responses** by oral or parenteral immunization with **ISCOMS**.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Oct) 25 (10) 2835-41.
Journal code: 1273201. ISSN: 0014-2980.

L10 ANSWER 66 OF 70 MEDLINE on STN DUPLICATE 30
AU Fernando G J; Stenzel D J; Tindle R W; Merza M S; Morein B; Frazer I H
TI Peptide polymerisation facilitates incorporation into **ISCOMs** and increases antigen-specific IgG2a production.
SO VACCINE, (1995) 13 (15) 1460-7.
Journal code: 8406899. ISSN: 0264-410X.

L10 ANSWER 67 OF 70 MEDLINE on STN DUPLICATE 31
AU Villacres-Eriksson M
TI Antigen presentation by naive macrophages, dendritic cells and B cells to primed T lymphocytes and their cytokine production following exposure to immunostimulating complexes.
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1995 Oct) 102 (1) 46-52.
Journal code: 0057202. ISSN: 0009-9104.

L10 ANSWER 68 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU REDDISH M A (Reprint); BUSZYNSKI V; DING L; LONGENECKER B M
TI ACTIVE SPECIFIC IMMUNOTHERAPY OF ADENOCARCINOMAS WITH SYNTHETIC TUMOR-ASSOCIATED ANTIGENS CONJUGATED TO KEYHOLE LIMPET HEMOCYANIN
SO ONKOLOGIE, (AUG 1995) Vol. 18, Supp. 1, pp. 33-35.
ISSN: 0378-584X.

L10 ANSWER 69 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU APOSTOLOPOULOS V; PIETERSZ G A; XING P X; LEES C J; MICHAEL M; BISHOP J; MCKENZIE I F C (Reprint)
TI THE IMMUNOGENICITY OF MUC1 PEPTIDES AND FUSION PROTEIN
SO CANCER LETTERS, (23 MAR 1995) Vol. 90, No. 1, pp. 21-26.
ISSN: 0304-3835.

L10 ANSWER 70 OF 70 MEDLINE on STN DUPLICATE 32
AU Valensi J P; Carlson J R; Van Nest G A
TI Systemic cytokine profiles in BALB/c mice immunized with trivalent influenza vaccine containing MF59 oil emulsion and other advanced **adjuvants**.
SO JOURNAL OF IMMUNOLOGY, (1994 Nov 1) 153 (9) 4029-39.
Journal code: 2985117R. ISSN: 0022-1767.

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L10 ANSWER 39 OF 70 MEDLINE on STN DUPLICATE 13
AU Moore A; McCarthy L; Mills K H
TI The **adjuvant** combination **monophosphoryl lipid A** and **QS21** switches T cell responses induced with a soluble recombinant HIV protein from Th2 to Th1.
SO VACCINE, (1999 Jun 4) 17 (20-21) 2517-27.
Journal code: 8406899. ISSN: 0264-410X.
AB The induction of protective immunity with recombinant vaccines is dependent on the identification of **adjuvant** or delivery systems that can augment immune responses, especially cellular immune responses, to soluble protein antigen. In this study we demonstrate that an **adjuvant** formulation comprising **QS21**, a purified form of saponin and 3D-**monophosphoryl lipid A** (MPL), a nontoxic derivative of lipopolysaccharide (LPS), enhances cellular and humoral immune responses to a recombinant HIV protein. Analysis of cytokine secretion by antigen-specific T-cells from the spleen demonstrated that **QS21** augmented **Th1** and Th2 **responses**, whereas addition of 3D-MPL resulted in preferential induction of type 1 T-cells. Furthermore, analysis of the subclass of the IgG antibody in the serum in mice immunized with gp120 with the combined **adjuvant** formulation confirmed the selective activation of Th1 cells in vivo. 3D-MPL was found to enhance B7-1 expression and IL-12 production by macrophages, which are known to be involved in the LPS-induced enhancement of **Th1 responses**. Thus 3D-MPL appears to act as an **adjuvant**, without the toxicity associated with LPS, by controlled and selective potentiating effects on antigen presentation and T-cell activation.

L10 ANSWER 40 OF 70 MEDLINE on STN DUPLICATE 14
AU Wong C P; Okada C Y; Levy R
TI TCR vaccines against T cell lymphoma: QS-21 and IL-12 **adjuvants** induce a protective CD8+ T cell response.
SO JOURNAL OF IMMUNOLOGY, (1999 Feb 15) 162 (4) 2251-8.
Journal code: 2985117R. ISSN: 0022-1767.
AB Tumor-specific TCR can serve as an effective target for active immunotherapy of T cell malignancies. Using the murine T cell tumor model C6VL, vaccination with C6VL TCR protected mice from a subsequent lethal dose of tumor cells. This study characterizes the immune mechanisms involved in the tumor protection, and the influence of immunologic **adjuvants** in inducing a protective immune response. Immune responses induced by TCR vaccines formulated with various **adjuvants**: QS-21, IL-12, **SAF**-1, CD40L, and GM-CSF were compared. QS-21, IL-12, and **SAF**-1 biased the humoral immune **response** toward **Th1**-type, reflected by the induction of IgG2a and IgG2b anti-C6VL TCR Abs. CD40L and GM-CSF exclusively produced IgG1 Abs, reflecting a Th2-type immune response. In our tumor model system, only vaccines containing **adjuvants** that induced a **Th1**-type immune **response** favored tumor protection. Furthermore, we demonstrated that CD8+ T cells were necessary and sufficient for tumor protection using anti-CD8 mAb depletion and adoptive cell transfer experiments. Transfer of hyperimmune serum containing anti-C6VL TCR Abs into na ive mice had modest anti-tumor effects and was

not sufficient to prevent tumor growth. TCR-vaccinated B cell-deficient mice were not protected against C6VL tumor, and tumor protection was not completely restored after hyperimmune serum transfer. Thus, B cells may serve as important APCs in inducing a protective immune response. Based on these results future TCR vaccines should be designed to maintain native TCR conformation, as well as induce a strong **Th1**-type immune **response**.

L10 ANSWER 41 OF 70 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AU Jiang, Baoming [Reprint author]; Estes, Mary K.; Barone, Christopher; Barniak, Vicki; O'Neal, Christine M.; Ottaiano, Adriana; Madore, H. Paul; Conner, Margaret E.
TI Heterotypic protection from rotavirus infection in mice vaccinated with virus-like particles.
SO Vaccine, (Feb., 1999) Vol. 17, No. 7-8, pp. 1005-1013. print.
CODEN: VACCDE. ISSN: 0264-410X.
AB Virus-like particles (VLPs) composed of rotavirus VP2, VP6, and VP7 of G1 or G3 serotype specificity were produced in insect cells coinfected with recombinant baculoviruses expressing single rotavirus genes. The VLPs were purified and subsequently evaluated for immunogenicity and protection in the adult mouse model of rotavirus infection. Mice were vaccinated twice intramuscularly with G1 VLPs formulated with Quillaja saponaria (QS-21) or adsorbed to aluminium hydroxide (AlOH), or with G1 VLPs alone. G3 VLPS, G1 plus G3 VLPs. inactivated SA11 virions formulated with QS-21, or **adjuvants** were similarly inoculated as controls. Mice were examined for serum and fecal antibody responses by ELISA or microneutralization assays. Protective efficacy of the VLP vaccine formulations against oral challenge with the G3 murine ECwt rotavirus was assessed by comparing the antigen shed in stool of the VLP-vaccinated mice to that of the **adjuvant**-immunized mice. G1 VLPs in QS-21 induced significantly higher serum and intestinal antibody titers than G1 VLPs in AlOH or G1 VLPs alone. QS-21 also heightened serum and fecal antibody responses to G3 VLPS. These QS-21-augmented antibody responses were further characterized by equivalent IgGi and IgG2a titers in sera, suggesting that G1 or G3 VLPs in QS-21 induced a balanced **Th1** /Th2 **response**. G1 VLPs in QS-21 induced partial protection (88%) against oral challenge with the heterotypic ECwt virus. whereas G1 VLPs in QS-21 induced complete protection (100%). In contrast. Gt VLPs when formulated with AlOH induced a predominant Th2 response and did not protect (1%) mice from virus challenge. Our results indicate that the type of **adjuvant** used clearly influences both antibody responses to rotavirus VLPs and the protective efficacy against rotavirus infections. These data have important implications for the development of parenteral vaccines to ameliorate rotavirus disease.

L10 ANSWER 42 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Heeney, Jonathan; Akerblom, Lennart; Barnett, Susan; Bogers, Willy; Davis, David; Fuller, Deborah; Koopman, Gerrit; Lehner, Thomas; Mooij, Petra; Morein, Bror; de Giuli Morghen, Carlo; Rosenwirth, Brigitte; Verschoor, Ernst; Wagner, Ralf; Wolf, Hans
TI HIV-1 vaccine-induced immune responses which correlate with protection from SHIV infection: compiled preclinical efficacy data from trials with ten different HIV-1 vaccine candidates
SO Immunology Letters (1999), 66(1-3), 189-195
CODEN: IMLED6; ISSN: 0165-2478
AB The specific immune mechanisms necessary and/or sufficient to elicit HIV-vaccine protection remain undefined. Utilizing the SHIV rhesus macaque model the immunogenicity as well as the efficacy of ten different HIV-1 vaccine candidates was evaluated. Comparison of the immune responses induced with the ability of the vaccine to protect from SHIV infection provided a means to det. which type of immune responses were necessary for protection. Vaccine candidates included VLPs, DNA, subunit protein with novel **adjuvant** formulations, **ISCOMs** and pox-virus vectors. Protection from SHIV infection was achieved in approx.

half of the animals which received a primary i.v. cell-free challenge. The presence of CTL in the absence of other effector responses did not correlate with protection from this route and type of challenge. Virus neutralizing antibodies (Nab) appeared to be necessary but alone were insufficient for protection. If Ag-specific IFN-.gamma. and/or IL-4 as well as lymphoproliferative (LP) responses were found with the lack of a detectable IL-2 response, then protection was not obsd. Immunity correlated with the magnitude of Nab responses, .beta.-chemokines and as well as balanced, qual. T-helper responses.

L10 ANSWER 43 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 15
AU Haigwood, Nancy L.; Pierce, Christopher C.; Robertson, Michael N.; Watson, Andrew J.; Montefion, David C.; Rabin, Michael; Lynch, John B.; Kuller, LaRene; Thompson, Jannelle; Morton, William R.; Benveniste, Raoul E.; Hu, Shiu-Lok; Greenbag, Philip; Mossman, Sally P.
TI Protection from pathogenic SIV challenge using multigenic DNA vaccines
SO Immunology Letters (1999), 66(1-3), 183-188
CODEN: IMLED6; ISSN: 0165-2478
AB To assess DNA immunization as a strategy for protecting against HIV infection in humans, the authors utilized SIVmne infection of Macaca fascicularis as a vaccine challenge model with moderate pathogenic potential. The authors compared the efficacy of DNA immunization alone and in combination with subunit protein boosts. All of the structural and regulatory genes of SIVmne clone 8 were cloned into mammalian expression vectors under the control of the CMV E-1 promoter. Eight M. fascicularis were immunized twice with 3 mg of plasmid DNA divided between two sites; i.m. and intradermal. Four primed macaques received a further two DNA immunizations at weeks 16-36, while the second group of four were boosted with 250 .mu.g recombinant gp160 plus 250 .mu.g recombinant gag-pol particles formulated in **MF-59 adjuvant**.
Half of the controls received four immunizations of vector DNA; half received two vector DNA and two **adjuvant** immunizations. As expected, humoral immune responses were stronger in the macaques receiving subunit boosts, but responses were sustained in both groups. Significant neutralizing antibody titers to SIVmne were detected in one of the subunit-boosted animals and in none of the DNA-only animals prior to challenge. T-cell proliferative responses to gp160 and to gag were detected in all immunized animals after three immunizations, and these responses increased after four immunizations. Cytokine profiles in PHA-stimulated PBMC taken on the day of challenge showed trends toward **Th1 responses** in 2t4 macaques in the DNA vaccinated group and in 1/4 of the DNA plus subunit vaccinated macaques; Th2 responses in 3/4 DNA plus subunit-immunized macaques; and Th0 responses in 4/4 controls. In bulk CTL culture, SIV specific lysis was low or undetectable, even after four immunizations. However, stable SIV gag-pol- and env-specific T-cell clones (CD3+CD8+) were isolated after only two DNA immunizations, and gag-pol- and nef-specific CTL lines were isolated on the day of challenge. All animals were challenged at week 38 with SIVmne uncloned stock by the intrarectal route. Based on antibody anamnestic responses (western, ELISA, and neutralizing antibodies) and virus detection methods (co-culture of PBMG and LNMC, nested set PCR- of DNA from PBMC and LNMC, and plasma QC-PCR), there were major differences between the groups in the challenge outcome. Surprisingly, sustained low virus loads were obsd. only in the DNA group, suggesting that four immunizations with DNA only elicited more effective immune responses than two DNA primes combined with two protein boosts. Multigenic DNA vaccines such as these, bearing all structural and regulatory genes, show significant promise and may be a safe alternative to live-attenuated vaccines.

L10 ANSWER 44 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU Rajananthanan P; Attard G S; Sheikh N A; Morrow W J W (Reprint)
TI Novel aggregate structure **adjuvants** modulate lymphocyte proliferation and Th1 and Th2 cytokine profiles in ovalbumin immunized

mice
SO VACCINE, (20 AUG 1999) Vol. 18, No. 1-2, pp. 140-152.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 0264-410X.
AB Cytokines are important mediators of effector lymphoid cell function during an immune response. The principal cytokine producers are the T helper (Th) cells and macrophages. Vaccine strategies need to take into account the balance of Th (Th1/Th2) cytokines they induce. **Adjuvants** are compounds that, when combined with an antigen, potentiate an immune response in an immunized species. The use of **adjuvants** has been shown to activate differentially Th1 and Th2 subsets. In this study we describe the immunopotentiating properties of three novel molecular aggregate formulations based on tomatine (RAMI), a glycosylamide lipid (RAM2) and a fifth generation dendrimeric polymer (RAM3) respectively. These formulations were evaluated for their ability to augment **Th1** or Th2 cytokine **responses** when administered with a soluble protein antigen. Of the three formulations. RAM1 was found to induce predominantly Th1 cytokines; the levels of which were substantially higher than those induced by reference control **adjuvants**. It was also found that at a late post-vaccinated period, RAMI can stimulate Th2 responses. In contrast, RAM2 and RAM3 induced cytokine profiles typically associated with Th2 responses.

L10 ANSWER 45 OF 70 MEDLINE on STN DUPLICATE 16
AU Mowat A M; Smith R E; Donachie A M; Furrie E; Grdic D; Lycke N
TI Oral vaccination with immune stimulating complexes.
SO IMMUNOLOGY LETTERS, (1999 Jan) 65 (1-2) 133-40.
Journal code: 7910006. ISSN: 0165-2478.
AB There is a need for non-living **adjuvant** vectors which will induce a full range of local and systemic immune responses to orally administered purified antigens. Here we describe our experience with lipophilic immune stimulating complexes (**ISCOMS**) containing the saponin **adjuvant** Quil A. When given orally, **ISCOMS** containing the model protein antigen ovalbumin (OVA) induce a wide range of systemic immune **responses**, including **Th1** and Th2 CD4 dependent activity, class I MHC restricted cytotoxic T-cell responses and local production of secretory IgA antibodies. More recent results indicate that **ISCOMS** may act partly by enhancing the uptake of protein from the gut. In addition, intraperitoneal injection of **ISCOMS** recruits and activates many components of the innate immune system. including neutrophils, macrophages, and dendritic cells. In parallel, there is increased production of nitric oxide (NO), reactive oxygen intermediates (ROI), interleukins (IL) 1, 6, 12, and gamma interferon (gammaIFN). Of these factors, only IL12 is essential for the immunogenicity of **ISCOMS** in vivo, as mucosal and systemic responses to **ISCOMS** are reduced in IL12KO mice, but not in IL4KO, IL6KO, inducible NO synthase (iNOS) KO, or gammaIFN receptor KO mice. We propose that **ISCOMS** act by targetting antigen and **adjuvant** to macrophages and/or dendritic cells. This pathway may be amenable to exploitation for vaccine development, especially if combined with another vector with a different mucosal **adjuvant** profile, such as cholera toxin.

L10 ANSWER 46 OF 70 MEDLINE on STN DUPLICATE 17
AU Morein B; Bengtsson K L
TI Immunomodulation by **iscoms**, immune stimulating complexes.
SO METHODS, (1999 Sep) 19 (1) 94-102. Ref: 88
Journal code: 9426302. ISSN: 1046-2023.
AB The iscom is a uniform stable complex consisting of cholesterol, phospholipid, **adjuvant**-active saponin, and antigen. The iscom matrix is a particulate complex with identical composition, shape, and morphology, but lacking the incorporated antigen. The assembly of the

complex is based on hydrophobic interactions, but antigens that are not hydrophobic can be conjugated with a hydrophobic tail or hidden hydrophobic regions can be exposed, e.g., by acid treatment, to facilitate the incorporation into **iscoms**. The functional aspects of **iscoms** are described emphasizing immunomodulation in mouse models. **Iscoms** prominently enhance the antigen targeting, uptake, and activity of antigen presenting cells including dendritic and B cells and macrophages resulting in the production of proinflammatory cytokines, above all interleukin (IL)-1, IL-6, and IL-12. The expression of costimulatory molecules major histocompatibility complex (MHC) class II, B7.1 and B7.2, is also enhanced. The latter partly explains why the iscom is an efficient **adjuvant** for elderly mice. **Iscoms** enhance the **Th1** type of **response** with increased production of IL-2 and interferon gamma. However, with some antigens and particularly in monkeys immunized with HIV **iscoms**, the production of IL-4 was enhanced. IL-4, IL-2, and interferon gamma (IFNgamma) together with the beta chemokines MIP-1alpha and MIP-1beta correlated with protection against challenge infection with a chimeric virus (simian immunodeficiency virus-human immunodeficiency virus). **Iscoms** were also shown to induce a potent immune response in the newborn and to be an efficient delivery system for mucosal administration. Technical information is given about formulation of **iscoms** and about handling of antigens to optimize their incorporation into **iscoms**.

L10 ANSWER 47 OF 70 CAPLUS
AU Van Pinxteren, Laurens A. H.; Bruce, Maureen G.; Campbell, Iris; Wood, Ann; Clarke, Christopher J.; Bellman, Anna; Morein, Bror; Snodgrass, David R.
TI Effect of oral rotavirus/iscom vaccines on immune responses in gnotobiotic lambs
SO Veterinary Immunology and Immunopathology (1999), 71(1), 53-67
CODEN: VIIMDS; ISSN: 0165-2427
AB A comparison of the effect on the immune responses in gnotobiotic lambs was made between an iscom vaccine prepd. from recombinant rotavirus VP6 protein, an inactivated rotavirus/iscommatrix vaccine and a vaccine comprising inactivated rotavirus alone. All three vaccines induced immunol. priming and some degree of protection was obsd. after a single oral dose. However, different immune responses were induced in response to a virulent infection. The group vaccinated with the rotavirus/iscom-matrix vaccine showed a Th2-like response characterized by rotavirus-specific antibodies and a down-regulation of IFN.gamma. in jejunal Peyer's patches. Both **Th1**-like and Th2-like immune **responses** were induced in the group receiving the VP6 vaccine as seen by significantly increased expressions of IFN.gamma. and IL-6 in the jejunal Peyer's patch together with an increased percentage of CD8+ T cells in the intestine and rotavirus-specific antibodies at mucosal surfaces. Iscom vaccines given orally have the ability to induce both **Th1**-like and Th2-like immune **responses** in a ruminant model.

L10 ANSWER 48 OF 70 CAPLUS
IN Cohen, Joseph
TI Vaccine composition against malaria
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
AB A vaccine compn. useful in the prevention or treatment of malaria comprises a plurality of malaria-derived antigens in combination with an **adjuvant** which is a preferential stimulator of **TH1** cell **response**.

L10 ANSWER 49 OF 70 CAPLUS
AU Sasaki, Shin; Sumino, Kaharu; Hamajima, Kenji; Fukushima, Jun; Ishii,

Norihisa; Kawamoto, Susumu; Mohri, Hiroshi; Kensil, Charlotte Read; Okuda, Kenji

TI Induction of systemic and mucosal immune responses to human immunodeficiency virus type 1 by a DNA vaccine formulated with QS-21 saponin **adjuvant** via intramuscular and intranasal routes

SO Journal of Virology (1998), 72(6), 4931-4939
CODEN: JOVIAM; ISSN: 0022-538X

AB Induction of mucosal and cell-mediated immunity is crit. for development of an effective vaccine against human immunodeficiency virus (HIV). The authors compared i.m. and intranasal immunizations with a DNA vaccine encoding env of HIV-1 and evaluated the QS-21 saponin **adjuvant** for augmentation of the systemic and mucosal immune responses to HIV-1 in a murine model. Vaccination via the two routes elicited comparable systemic immune responses, and QS-21 consistently enhanced antigen-specific serum IgG2a prodn., delayed-type hypersensitivity reaction, and cytolytic activity of splenocytes. Intestinal secretory IgA prodn. and cytolytic activity of the mesenteric lymph node cells are preferentially elicited by intranasal immunization, and QS-21 augmented these activities as well. This **adjuvant** augmented prodn. of interleukin-2 (IL-2) and gamma interferon (IFN-.gamma.) assocd. with decrease in IL-4 synthesis by antigen-restimulated splenocytes. The serum Ig subtype profile showed a dominant IgG2a response and less strong IgG1 and IgE prodn. in a QS-21 dose-dependent manner. As expected, enhancements of humoral and cell-mediated immune responses by QS-21 were abrogated by treatment with anti-IL-2 and anti-IFN-.gamma. monoclonal antibodies. These results suggest that the intranasal route of DNA immunization is more efficient than the i.m. route in inducing mucosal immunity mediated by sIgA and mesenteric lymphocytes. Furthermore, QS-21 is able to act as a mucosal **adjuvant** in DNA vaccination and demonstrates its immunomodulatory property via stimulation of the Th1 subset. This study emphasizes the importance of the route of immunization and the use of an **adjuvant** for effective DNA vaccination against HIV-1.

L10 ANSWER 50 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN

AU Sjolander, Anders; Baldwin, Tracey M.; Curtis, Joan M.; Handman, Emanuela

TI Induction of a **Th1** immune **response** and simultaneous lack of activation of a Th2 response are required for generation of immunity to leishmaniasis

SO Journal of Immunology (1998), 160(8), 3949-3957
CODEN: JOIMA3; ISSN: 0022-1767

AB Exptl. systems based on immunization with plasmid DNA or immune-stimulating complexes were used to delineate the requirements for generation of protective immunity against murine leishmaniasis. Vaccination with plasmid DNA encoding the host-protective Leishmania major parasite surface Ag-2 primed for an essentially exclusive **Th1** **response** that protected mice against L. major infection. In contrast, parasite surface Ag-2 in immune-stimulating complexes generated an immune **response** with mixed **Th1**-like and Th2-like properties that was not protective despite the activation of CD4+ T cells secreting IFN-.gamma.. These results indicate that a **Th1** **response** is sufficient to protect against cutaneous leishmaniasis, but the induction of a simultaneous Th2 **response** abrogates the **Th1** effector function. DNA vaccines may therefore have an advantage for diseases in which protection depends on the induction of **Th1** **responses**.

L10 ANSWER 51 OF 70 MEDLINE on STN DUPLICATE 18

AU Sjolander A; Baldwin T M; Curtis J M; Bengtsson K L; Handman E

TI Vaccination with recombinant Parasite Surface Antigen 2 from Leishmania major induces a **Th1** type of immune **response** but does not protect against infection.

SO VACCINE, (1998 Dec) 16 (20) 2077-84.
Journal code: 8406899. ISSN: 0264-410X.

AB Vaccination with the native Parasite Surface Antigen 2 of Leishmania major with Corynebacterium parvum as **adjuvant** protects mice from leishmaniasis through a **Th1** mediated **response**. Here we show that vaccination with a recombinant form of this protein, purified from Escherichia coli and administered in **iscoms** or with C. parvum as **adjuvant**, does not induce protective immunity despite the induction of **Th1 responses**. The results suggest that protective immunity depends on the ability of the vaccinating antigen to induce Th1-like T cells with ability to be recalled by infection. Therefore, the conformation of antigens may play a more major role for the induction of T cell mediated immunity than originally considered.

L10 ANSWER 52 OF 70 MEDLINE on STN DUPLICATE 19
AU Newman K D; Sosnowski D L; Kwon G S; Samuel J
TI Delivery of MUC1 mucin peptide by Poly(d,l-lactic-co-glycolic acid) microspheres induces type 1 T helper immune responses.
SO JOURNAL OF PHARMACEUTICAL SCIENCES, (1998 Nov) 87 (11) 1421-7. Journal code: 2985195R. ISSN: 0022-3549.
AB Synthetic peptides corresponding to the variable tandem repeat domain of the cancer-associated antigen MUC1 mucin are candidates for cancer vaccines. In our investigation mice were immunized via subcutaneous injection with poly(d,l-lactic-co-glycolic acid) (PLGA) microspheres containing a MUC1 mucin peptide. It was hypothesized that microencapsulation of the MUC1 mucin peptide would prime for antigen-specific **Th1 responses** while avoiding the need for traditional **adjuvants** and carrier proteins. Furthermore, an immunomodulator, **monophosphoryl lipid A** (MPLA), was incorporated into the peptide-loaded PLGA microspheres based on its ability to enhance **Th1 responses**. The results revealed T cell specific immune responses. The cytokine secretion profiles of the T cells consisted of high levels of interferon-gamma with undetectable levels of interleukin-4 and interleukin-10. Moreover, incorporation of MPLA in the MUC1 peptide-loaded PLGA microspheres resulted in an increase in interferon-gamma production. The antibody response was negative for IgM and IgG in the absence of MPLA; however, in the presence of MPLA antibody production was negative for IgM with a minimal IgG response consisting of IgG2a, IgG2b, and IgG3. Based on the antibody and cytokine profiles, it was concluded that MUC1 mucin peptide-loaded PLGA microspheres are capable of eliciting specific **Th1 responses**, which may be enhanced through the use of MPLA.

L10 ANSWER 53 OF 70 CAPLUS COPYRIGHT 2003 ACS on STN
AU Papadopoulou, Georgia; Karagouni, Evdokia; Dotsika, Eleni
TI **ISCOMs** vaccine against experimental leishmaniasis
SO Vaccine (1998), 16(9/10), 885-892
CODEN: VACCDE; ISSN: 0264-410X
AB The major surface glycoprotein (gp63) of Leishmania major incorporated into the immunostimulating complexes (**ISCOMs**) was used to protect Balb/c mice against exptl. infection. Two i.p. vaccinations with low doses of gp63 into **ISCOMs** (gp63-**ISCOMs**) induced protective immunity in vaccinated mice as indicated by reduced inflammation and suppressed lesions after exptl. challenge. An augmented IgG-specific secretion and a specific switching towards the IgG2a isotype was obsd. in the serum of vaccinated mice. Gp63-**ISCOMs** primed spleen cells restimulated in vitro with sol. Leishmania antigen (SLA) or live parasites displayed strong gp63-specific proliferative responses and secreted high levels of interleukin-2, interferon .gamma., and interleukin-10 but not interleukin-4. No delayed type hypersensitivity response to either SLA or LV39 was detected. Thus, gp63-**ISCOMs** induced a protective immunity in the susceptible Balb/c mice against Leishmania challenge, modulating the immune **response** towards a **Th1** rather than Th2 type.

L10 ANSWER 54 OF 70 MEDLINE on STN DUPLICATE 20
AU Morein F; Bengtsson K L
TI Functional aspects of **iscoms**.
SO IMMUNOLOGY AND CELL BIOLOGY, (1998 Aug) 76 (4) 295-9. Ref: 29
Journal code: 8706300. ISSN: 0818-9641.
AB The iscom is a delivery system, designed for both parenteral and mucosal modes of administration, for both antigens and **adjuvants**, components which are interchangeable. By the parenteral route a prominent systemic **Th1** type of **response** is evoked, but the mucosal immunoglobulin A (IgA) response was insignificant. Intranasal (i.n.) immunization with **iscoms** evoked potent mucosal IgA response and serum IgG which was much higher than that induced by i.n. administration of the B subunit of cholera toxin (rCTB), both to rCTB itself as well as to co-administered antigen. The immunomodulatory effect on rCTB or co-administered antigens imposed by the iscom was demonstrated by a potent mucosal IgA switch and an enhanced IgG2a serum response. The incorporation of a targeting molecule in the iscom enhanced the remote IgA response in the genital tract mucosa. The capacity to induce CD8-restricted cytotoxic T lymphocytes (CTL) is unique for the iscom as a nonreplicating system, which is facilitated by the delivery of antigens to the cytosol. The immunomodulatory capacity of **iscoms** also paved the way to override the inhibitory effect of maternally derived antibodies and the relative unresponsiveness of an immature neonatal immune system.

L10 ANSWER 55 OF 70 MEDLINE on STN DUPLICATE 21
AU Smith R E; Donachie A M; Mowat A M
TI Immune stimulating complexes as mucosal vaccines.
SO IMMUNOLOGY AND CELL BIOLOGY, (1998 Jun) 76 (3) 263-9. Ref: 63
Journal code: 8706300. ISSN: 0818-9641.
AB There is a need for non-living **adjuvant** vectors that will allow a full range of local and systemic immune responses to orally administered purified antigens. Here we describe our experience with lipophilic immune-stimulating complexes (**ISCOMs**) containing the saponin **adjuvant** Quil A. When given orally, **ISCOMs** containing the model protein antigen ovalbumin (OVA) induce a wide range of systemic immune **responses**, including **Th1** and Th2 CD4-dependent activity, serum IgG antibodies and class I MHC-restricted cytotoxic T cell responses. In addition, there is local production of secretory IgA antibodies in the intestine itself, as well as priming of CD4 and CD8 T cell responses in the draining lymphoid tissues. Preliminary results indicate that the mucosal **adjuvant** properties of **ISCOMs** may reflect their ability to deliver antigen combined with the pro-inflammatory properties of Quil A in a particulate form. Of the many inflammatory mediators induced, interleukin-12, derived from dendritic cells and/or macrophages, appears to be of central importance. These results indicate that **ISCOMs** may prove to be useful mucosal vaccine vectors with functions which are distinct from existing vectors of this type.

L10 ANSWER 56 OF 70 MEDLINE on STN DUPLICATE 22
AU Newman K D; Samuel J; Kwon G
TI Ovalbumin peptide encapsulated in poly(d,l lactic-co-glycolic acid) microspheres is capable of inducing a T helper type 1 immune response.
SO JOURNAL OF CONTROLLED RELEASE, (1998 Jun) 54 (1) 49-59.
Journal code: 8607908. ISSN: 0168-3659.
AB An ovalbumin (OVA) peptide, consisting of residues 323-339, was incorporated into poly(d,l lactic-co-glycolic acid) (PLGA) microspheres and administered to mice. It was hypothesized that microencapsulation of the peptide in PLGA microspheres would avoid the need for traditional **adjuvants** and bias the immune **respons** towards a type 1 T helper (**Th1**) **response**. An immunomodulator, **monophosphoryl lipid A** (MPLA), was incorporated into the microspheres to determine its efficacy in enhancing a **Th1 response**. The specificity of the immune

response was determined using a T cell proliferation assay. The type of T helper response was determined by analysis of the cytokine secretion profiles of the proliferating T cells. Following s.c. immunization, the results revealed a T cell-specific immune response for the encapsulated OVA peptide both with and without MPLA. The cytokine profiles revealed high levels of IFN-gamma with very low levels of IL-4 and IL-10, suggesting a **Th1 response**. Furthermore, incorporation of MPLA in the peptide loaded PLGA microspheres resulted in an increase in the production of IFN-gamma. Hence, peptide-loaded PLGA microspheres are capable of eliciting a specific **Th1** immune **response**, which may be further enhanced in the presence MPLA.

L10 ANSWER 57 OF 70 MEDLINE on STN DUPLICATE 23
AU Morein B; Villacres-Eriksson M; Lovgren-Bengtsson K
TI Iscom, a delivery system for parenteral and mucosal vaccination.
SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1998) 92 33-9. Ref: 16
Journal code: 0427140. ISSN: 0301-5149.
AB The iscom is a supramolecular spherical structure, about 40nm in diameter, built up by structure-forming and immunomodulating quillaja triterpenoids, lipids and antigens. **Iscoms** with a defined quillaja triterpenoid formulation named QH 703 are in human trials. The advantages of using the particulate iscom form of quillaja components are (i) that local reactions at the site of injection can be avoided; a manifold higher dose of quillaja components in **iscoms** than in free form can be injected without causing side effects; (ii) considerably lower doses of both quillaja components and antigens are required to obtain a certain level of immune response. The iscom particle targets the antigen and **adjuvant** components to both the endosomal and cytosolic pathways for antigen presentation, resulting in both MHC class I and class II restricted immune responses. Further, **iscoms** induce APC to produce IL-1, IL-6 and IL-12 and a **TH1** type of **response** with enhanced IL-2 and IFN-gamma production. **Iscoms** are now constructed to target the mucosal lymphatic systems. **Iscoms** administered intranasally induce secretory IgA responses in lungs and distant mucosal membranes e.g. in the genital tract.

L10 ANSWER 58 OF 70 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AU Sjolander A (Reprint); Bengtsson K L; Morein B
TI Kinetics, localization and cytokine profile of T cell responses to immune stimulating complexes (**iscoms**) containing human influenza virus envelope glycoproteins
SO VACCINE, (JUN 1997) Vol. 15, No. 9, pp. 1030-1038.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, OXON, ENGLAND OX5 1GB.
ISSN: 0264-410X.
AB Immune stimulating complexes (**iscoms**) are 40 nm particles combining **adjuvant**-active Quillaja saponins and multimeric presentation of antigens. The distribution in mice of influenza virus **iscoms** and the resulting T cell responses in the lymph nodes (LN) and spleen were characterized After a single subcutaneous injection, **iscoms** were delivered to the draining LN where they induced a transient population of LN cells which responded with proliferation and secretion of interleukin-2 (IL-2), gamma-interferon (IFN-gamma) and interleukin-4 (IL-4) after restimulation. The response in the spleen developed more slowly, sustained for 12 weeks and was characterized by cells producing in particular IL-2 and IFN-gamma but also IL-4. A booster resulted in a dramatic enhancement of the production of IFN-gamma, indicating that **iscoms** efficiently recruit cells with **Th1** properties. Con?parisons of T cell **responses** to **iscoms** and to influenza virus antigen in Freund's complete **adjuvant**,!ant demonstrate that these **adjuvants** affect both the localization and cytokine profile of T cell responses. (C) 1997 Elsevier Science Ltd.

L10 ANSWER 59 OF 70 MEDLINE on STN DUPLICATE 24
AU Ahluwalia A; Gokulan K; Nath I; Rao D N
TI Modification of delivery system enhances MHC nonrestricted immunogenicity of V3 loop region of HIV-1 gp120.
SO MICROBIOLOGY AND IMMUNOLOGY, (1997) 41 (10) 779-84.
Journal code: 7703966. ISSN: 0385-5600.
AB A successful peptide vaccine for AIDS is desired to elicit T-helper and cytotoxic T lymphocyte responses besides neutralizing antibodies. The V3 loop peptide of HIV-1 has been shown to contain the principal neutralizing domain, one of the most immunodominant regions, having both B-cell and T-cell determinants. In this study, the tip of the V3 loop region was mutated from GPGR to GPGQ based on the sequence of Indian isolates (CKRKIHIGPGQAFYT). To further enhance the immunogenicity of this epitope, two delivery systems of immune stimulating complexes (**ISCOMs**) and liposomes were used to incorporate the peptide. Mice of differing haplotypes, H-2b, H-2d, H-2k and H-2s, showed no MHC restriction when immunized with these formulations. The IgG levels as assessed by ELISA were found to be significantly higher ($P < 0.05$ to $P < 0.001$) for even five-fold lower doses of the peptide in **ISCOMs** and liposomes as compared to the conventional alum-based preparation. The major subtype elicited was IgG2a/IgG2b, suggestive of a **Th1**-like **r sponse** for all the formulations. Thus, it would appear that the same peptide incorporated in **ISCOMs** and liposomes selects a **Th1 response** and may therefore be important not only for neutralization but also for virus clearance.

L10 ANSWER 60 OF 70 MEDLINE on STN DUPLICATE 25
AU Dotsika E; Karagouni E; Sundquist B; Morein B; Morgan A; Villacres-Eriksson M
TI Influence of Quillaja saponaria triterpenoid content on the immunomodulatory capacity of Epstein-Barr virus **iscoms**.
SO SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1997 Mar) 45 (3) 261-8.
Journal code: 0323767. ISSN: 0300-9475.
AB The immune responses to immunostimulating complexes (**iscoms**) containing recombinant Epstein-Barr virus (EBV) gp340 envelope protein was evaluated in BALB/c (H-2(d)) and CBA (H-2(k)) mice. Gp340-**iscoms** were used either with a low content of Quillaja triterpenoid **adjuvant** (L-**iscoms**) or supplemented with additional Quillaja **adjuvant** in the form of iscomatrix (S-**iscoms**). Class and subclass distribution of anti-gp340 antibodies, EBV-neutralizing antibodies, antigen-specific T cell proliferation and cytokine production were determined and these results compared to those obtained by immunization with non-adjuvated gp340. The H-2(d) and H-2(k) mice were characterized as low or high responders in respect to the level of specific anti-gp340 antibodies, secretion of IgG2a isotype, antigen-specific lymphoproliferative capacity, interferon-gamma (IFN-gamma) and interleukin-10 (IL-10) production in the basic immunizations with gp340. While presentation of the antigen in iscom formulations with low levels of Quillaja triterpenoids induces a moderate enhancement of the immune responses in the low responder H-2(d) mice, supplementation with high levels of iscomatrix immunomodulator was required to enhance the immune responses in the high responder H-2(k) mice. In both mouse strains subcutaneous immunization with S-**iscoms** resulted in a significant increase of IgG1- and IgG2a-specific antibodies, as well as in strong antigen-specific proliferative response confirmed by the simultaneous cytokine production. The enhanced antigen-specific secretion of IL-2 and IFN-gamma together with the abrogation of IL-10 and the absence of IL-4 indicates that the **responses** were driven towards a **Th1**-type rather than Th2-type immune **response**. The S-iscom formulations minimized the differences in immune responses between the two mouse strains, but the capacity of immune sera to neutralize EBV transformation in vitro remained completely strain-dependent. These data indicate that immune responses generated by **iscoms** can be manipulated by altering the

triterpenoid composition of the **iscoms** and that the levels of triterpenoids can determine whether or not a **Th1**-type **response** is made.

L10 ANSWER 61 OF 70 MEDLINE on STN DUPLICATE 26
AU Villacres-Eriksson M; Behboudi S; Morgan A J; Trinchieri G; Morein B
TI Immunomodulation by Quillaja saponaria **adjuvant** formulations: in vivo stimulation of interleukin 12 and its effects on the antibody response.
SO CYTOKINE, (1997 Feb) 9 (2) 73-82.
Journal code: 9005353. ISSN: 1043-4666.
AB The capacity of **adjuvants** to activate Ag-presenting cells during the induction of the primary immune response is of critical importance for the development of protective immunity to a number of pathogens. In this context, interleukin 12 (IL-12) has a key role by controlling the differentiation of T helper cells and favouring the expansion of Th1 cells. The capacity of **iscoms** with influenza virus Ag (flu-**iscoms**) and iscom matrix with EBV gp340 Ag to induce IL-12 was analysed in mice. The flu-iscom drives the immune **response** towards a **Th1** type subsequent to IL-12 induction as measured in the serum of H2b, H2d and H2k mice. The iscom presenting the Ag and **adjuvant** in the same particle was considerably more efficient than the formulation of matrix and Ag in separate particles. Inhibition experiments with mAb neutralizing IL-12, interferon gamma (IFN-gamma) or IL-4, the latter two cytokines representing the **Th1** and Th2 type of **responses**, showed that **iscoms** induce a broader immune response than that involving IL-12. This was shown by the additional effect that IL-4 neutralization had on the immune response to **iscoms**. Anti-IL 12 reduced the specific total Ab as well as IgG1, IgG2a and IgG2b while anti-IL 4 influenced the response to iscom by decreasing IgG2a and increasing IgG1. Further, the neutralization experiments indicate that IL-12 has a broader effect than IFN-gamma on the Ab response by influencing the production of IgG1, IgG2a and IgG2b.

L10 ANSWER 62 OF 70 MEDLINE on STN DUPLICATE 27
AU Sjolander A; van't Land B; Lovgren Bengtsson K
TI **Iscoms** containing purified Quillaja saponins upregulate both **Th1**-like and Th2-like immune **responses**.
SO CELLULAR IMMUNOLOGY, (1997 Apr 10) 177 (1) 69-76.
Journal code: 1246405. ISSN: 0008-8749.
AB The immune stimulating complex (iscom) is built up by antigen, cholesterol, phospholipids, and **adjuvant** active Quillaja saponins. Previous studies have shown that **iscoms** containing Quil A (a semipurified preparation of saponins) efficiently induce antibody and cell-mediated immune responses. In this study, we demonstrate that **iscoms** containing a mixture of two purified low toxicity Quillaja saponin fractions (ISCOPREP 703) are able to upregulate both **Th1**-like and Th2-like immune **responses**. Thus, ovalbumin (OVA) **iscoms** induced higher levels of antigen-specific IgG1 and IgG2a antibodies and increased the production of both IFN-gamma and IL-4 compared with OVA administered without **adjuvant**. In contrast, OVA formulated in Al(OH)3 elicited IgG1 and IgE antibodies and primed spleen cells producing IL-4 and IL-10, suggesting the activation of primarily Th2-like cells. These findings underline that **adjuvants** are able to alter the character of immune responses and may be used to generate responses with desired properties.

L10 ANSWER 63 OF 70 MEDLINE on STN DUPLICATE 28
AU Noll A; AutenriethIB
TI Immunity against Yersinia enterocolitica by vaccination with Yersinia HSP60 immunostimulating complexes or Yersinia HSP60 plus interleukin-12.
SO INFECTION AND IMMUNITY, (1996 Aug) 64 (8) 2955-61.
Journal code: 0246127. ISSN: 0019-9567.
AB Microbial heat shock proteins (HSP) are dominant antigens for the host

immune response. Because of the high sequence homology between mammalian and microbial HSP, their value as component of a subunit vaccine has been the subject of controversy. Previous work from this laboratory, however, demonstrated for the first time that the adoptive transfer of HSP60-reactive CD4+ alphabeta T-cell clones confers protection against bacterial infection in mice but does not induce autoimmunity. In the present study, we have therefore evaluated the potential role of Yersinia HSP60 (Y-HSP60) as a vaccine in the Yersinia enterocolitica mouse infection model. For this purpose, immunostimulating complexes (ISCOM) which included Y-HSP60 were constructed. Parenteral administration of this vaccine induced high Y-HSP60-specific serum antibody responses as well as T-cell responses. This reaction was parallelled by immunity against a lethal challenge with Y. enterocolitica. In contrast, mucosal application of Y-HSP60-ISCOM failed to induce systemic Y-HSP60-specific T-cell responses and thus failed to induce immunity against yersiniae. Likewise, vaccination with purified recombinant Y-HSP60 induced antibody responses but only weak T-cell responses. Therefore, this vaccination protocol was not protective. However, when interleukin-12 was used as an **adjuvant**, purified Y-HSP60 induced significant Y-HSP60-specific T-cell responses and thus induced protection against subsequent challenge with yersiniae. These studies suggest that (i) microbial HSP might be promising candidates for the design of subunit vaccines and (ii) interleukin-12 is an efficient alternative **adjuvant** to ISCOM particles for induction of protective CD4 **Th1**-cell-dependent immune **responses** against bacterial pathogens.

L10 ANSWER 64 OF 70 MEDLINE on STN
AU Gupta R K; Varanelli C L; Griffin P; Wallach D F; Siber G R
TI **Adjuvant** properties of non-phospholipid liposomes (Novasomes) in experimental animals for human vaccine antigens.
SO VACCINE, (1996 Feb) 14 (3) 219-25.
Journal code: 8406899. ISSN: 0264-410X.
AB Non-phospholipid liposomes composed of dioxyethylene cetyl ether, cholesterol and oleic acid were evaluated as **adjuvants** with human vaccine antigens, tetanus toxoid (TT) and diphtheria toxoid (DT), in mice and rabbits. Antigens encapsulated in or mixed with liposomes elicited antitoxin levels similar to those elicited by antigens given with Freund's **adjuvant** or adsorbed onto aluminum phosphate. All liposomal antigen preparations, antigen given with Freund's **adjuvant** or adsorbed onto aluminum phosphate, elicited significantly higher IgG antibodies and antitoxin levels than soluble antigens in mice after a single injection and in rabbits after each of three injections. TT encapsulated in liposomes elicited sustained anti-TT IgG antibody levels in mice after a single injection as compared to TT mixed with liposomes. TT mixed with or encapsulated within liposomes containing **monophosphoryl lipid A**/squalene or squalene alone, as well as aluminum phosphate adsorbed TT elicited greater primary responses in mice than TT mixed with or encapsulated within plain liposomes. Liposomal TT preparations produced a slightly higher anamnestic response in mice than aluminum phosphate adsorbed TT. Subclass analysis of anti-TT antibodies showed that the majority of the antibodies belong to IgG1 subclass. Liposomal TT preparations, particularly those with encapsulated **monophosphoryl lipid A**/squalene or squalene alone, consistently elicited higher levels of anti-TT IgG2a and IgG2b than aluminum phosphate adsorbed or soluble TT. None of the preparations elicited IgG3 or IgM antibodies. It appears that non-phospholipid liposomes are as potent **adjuvants** as the currently employed **adjuvant** for human vaccines (aluminum phosphate) or a benchmark **adjuvant** for experimental immunology (Freund's **adjuvant**), and may be able to modulate the immune **response** towards the **Th1** type.

L10 ANSWER 65 OF 70 MEDLINE on STN DUPLICATE 29
AU Maloy K J; Donachie A M; Mowat A M

TI Induction of **Th1** and Th2 CD4+ T cell **responses** by oral or parenteral immunization with **ISCOMS**.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Oct) 25 (10) 2835-41.
Journal code: 1273201. ISSN: 0014-2980.

AB We examined the ability of oral or parenteral immunization with immune stimulating complexes containing ovalbumin (**ISCOMS**-OVA) to prime T cell proliferative and cytokine responses. A single subcutaneous immunization with **ISCOMS**-OVA primed potent antigen-specific proliferative responses in the draining popliteal lymph node, which were entirely dependent on the presence of CD4+ T cells. CD8+ T cells did not proliferate in vitro even in the presence of the appropriate peptide epitope and exogenous interleukin (IL)-2. Primed popliteal lymph node cells produced IL-2, IL-5 and interferon (IFN)-gamma, but not IL-4 when restimulated with OVA in vitro. Serum antigen-specific IgG1 and IgG2a antibody responses were also primed by subcutaneous immunization with **ISCOMS**-OVA, confirming the stimulation of both Th1 and Th2 cells in vivo. Spleen cells from subcutaneously primed mice produced a similar pattern of cytokines, indicating that disseminated priming had occurred. Oral immunization with **ISCOMS**-OVA also primed local antigen-specific proliferative responses in the mesenteric lymph node and primed an identical pattern of systemic cytokine responses in the spleen. The ability of **ISCOMS** to prime both **Th1** and Th2 CD4+ T cell **responses** may be central to their potent **adjuvant** activities and confirm the potential of **ISCOMS** as future oral vaccine vectors.